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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,330	04/25/2005	Peter'Carmeliet	50304/056001	3636

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
09/27/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/519,330	CARMELIET ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14-16 and 19-22* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15,16 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 13 July 2007 has been entered in full. Claims 2-13, 17 and 18 are canceled. Claim 14 is withdrawn. New claims 19-22 are added.

Claims 1, 15, 16, 19-22 are under examination.

Withdrawn Objections And/Or Rejections

The rejection to claims 1, 10, 15-17 under 35 U.S.C. 103(a) as being unpatentable over Murakami et al. (JP 2001086982 A, translated document provided) in view of Robinson et al. (FASEB, Vol. 15, pages 1215-1217, May 2001) and Dias et al. (PNAS, Vol. 98, No. 19, pages 10857-10862, Sept. 2001), as set forth at pages 8-10 of the previous Office Action (13 April 2007), is *withdrawn* in view of the amendment (13 July 2007).

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 15, 16 (and new claims 19-22) remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

"...method comprising administering **an anti-placental growth factor antibody or functionally active fragment thereof...**"

does not reasonably provide enablement for:

"...method comprising administering **an antibody or a functionally active fragment thereof, antisense nucleic acids against placental growth factor, interference RNA against placental growth factor, ribozymes against placental growth factor and a tetrameric peptide that binds specifically to placental growth factor...**"

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pages 3-6 of the previous Office Action (13 April 2007).

Applicant argues that tetrameric peptide antagonists interacting specifically with PIGF are disclosed in Example 10 of WO 01/85796, which is incorporated by reference into the current application. Applicant argues that antisense nucleic acid against placental growth factor are described in Yonekura et al. {Journal of Biological Chemistry 274:35172-8,1999}. Applicant argues that Yonekura et al. demonstrate that the administration of antisense nucleic acids against the PIGF gene was capable of reducing the level of PIGF-1 and PIGF-2 in endothelial cells. Applicant cites page 35176, left column, first paragraph. Applicant argues that this shows that antisense nucleotides are effective antagonists. Applicant argues that interference RNA and ribozymes behave similarly to antisense RNA to inhibit the activity of PIGF. Applicant cites pages in the specification. Applicant maintains that it would not require undue experimentation to employ antagonist of PIGF as claimed.

Applicant's arguments have been fully considered but are not deemed persuasive. Firstly, tetrameric peptides binding on PIGF can include any peptide that can bind PIGF. An "antibody or a functionally active fragment thereof" instead of "anti-PIGF antibodies or a functionally active fragment thereof" encompasses any antibody which is capable of binding PIGF. The specification does not address how to make and use *any* molecule that would bind or affect the binding and/or signaling activity of PIGF to reduce bone resorption or treat osteoporosis in an individual. The instant specification fails to indicate that a representative number of structurally related compounds are disclosed and therefore, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claim and would not know how to make them. Secondly, Yonekura et al. teach that the administration of antisense nucleic acids against the PIGF gene was capable of reducing the level of PIGF-1 and PIGF-2 in endothelial cells *in vitro*. Example 10 in WO 01/85796 only teaches the isolation of PIGF inhibitors by screening a tetrameric library. It could not be predicted that the cell culture data presented in Yonekura et al. or in the data presented in WO 01/85796 would be in any way correlative with **therapeutic PIFG antagonist agents for *in vivo* treatment of bone resorption or osteoporosis.** Murakami et al. (reference of record) teach that when anti-VEGF antibody was administered to mice, the number of osteoclast was reduced. The instant specification, however, fails to teach that antisense nucleotides, interference RNA and ribozymes against PIGF or tetrameric peptides are effective antagonists *in vivo*. The specification fails to teach or disclose examples regarding the amounts and/or routes of

administration of this pharmaceutical composition for treatment of bone resorption/osteoporosis in animal models. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of working examples, however is a factor to be considered, especially in a case involving an unpredictable art such as *in vivo* administration of nucleic acid, RNA, gene therapy, etc. The experimentation is not routine and the specification has provided little or no guidance.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Written description

Claims 1, 15, 16 (and new claims 20 and 22) remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The basis for this rejection is set forth at pages 6-8 of the previous Office Action (13 April 2007).

Applicant argues that there is no doubt that the specification allows the person of ordinary skill in the art to recognize what is claimed. Applicant argues that there can be no question that one of ordinary skill would readily recognize PIGF antagonist, as encompassed by the present set of claims. Applicant maintains that all of the antagonists used for practicing the claimed methods were either available in the art or could be produced by standard techniques at the time of filing, based on the known

nucleic acid (antisense, interference RNA and ribozymes) or protein sequence (e.g. antibodies and tetrameric peptides) of placental growth factor. Applicant argues that in view of their structure-function relationship to the placental growth factor nucleic acid or protein sequence, PIGF antagonist were readily recognized as such by the skilled person. Applicant submits that as all of the claimed antagonist exert their effect in the same way (i.e., reduce functional PIGF levels leading to the reduction of bone resorption.

Applicant's arguments have been fully considered but are not deemed persuasive. The protein sequence of PIGF is known, however, the recitation, "an antagonist of placental growth wherein said antagonist is an antibody or a functionally active fragment thereof" instead of "anti-PIGF antibodies or a functionally active fragment thereof" encompasses **any antibody**, which is capable of binding PIGF and reducing bone resorption. The specification fails to disclose the structural characteristics of *all antibodies that are capable of binding PIGF and reducing bone resorption.* A tetrameric peptide antagonist that binds specifically to placental growth factor encompasses any type of tetrameric peptide that binds specifically to placental growth and reduces bone resorption. *The specification fails to disclose the structural characteristics of any tetrameric peptide that is capable of binding PIGF and reducing bone resorption.* **The instant claims are drawn to a genus of PIGF antagonist based entirely on the function of reducing bone resorption.** There is no evidence that there is any structure/function relationship of the tetrameric peptide antagonists or the antibody antagonists identified by the action of reducing bone resorption. That is to

say; **a PIGF tetrameric peptide antagonist identified via the action of reducing bone resorption is not representative of the structure of the entire group of PIGF tetrameric peptide antagonists that might be found. An antibody or functionally active fragment thereof identified via the action of reducing bone resorption is not representative of the structure of the entire group of antagonist antibodies or functionally active fragments thereof that might be found.** There is no structural element correlative with the function, nor is there any indication that Applicant is in possession of any PIGF antagonist (i.e. tetrameric, antibody). Thus, there is insufficient descriptive support for the instant genus. The courts have specifically stated that the skilled artisan cannot envision the *detailed chemical structure* of an encompassed molecule until the structure is disclosed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. Due to the breadth of the claim genus and lack of the definitive structural features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Applicant was in possession of the claimed genus.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

NEW CLAIM REJECTIONS/OBJECTIONS

Claim Rejections-35 USC § 112, First Paragraph, Written Description (New Matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed: "a method for reducing bone resorption in an individual **exhibiting low bone mass or decreased bone mineral density**....".

Applicant's amendment, filed 13 July 2007, asserts that no new matter has been added and directs support to page 1, lines 4-8 and page 2, lines 18-20 for the written description for the above-mentioned "limitations". The specification on page 1, lines 4-8 states, "this invention relates to antagonists of placental growth factor and signaling thereof, pharmaceutical compositions containing such antagonists and the use of such antagonists to prevent bone loss or bone mass and to enhance bone healing including the treatment of conditions which present with low bone mass and/or bone defects in vertebrates, and particularly mammals, including humans". The specification on page 2, lines 18-20 state, "an object of the present invention is to provide a medicament for the treatment of osteoporosis in higher mammals exhibiting decreased cortical bone mineral

density and preventing osteoporosis due to cortical bone mineral density reduction in such mammals".

Applicant's arguments have been fully considered but are not found persuasive. The instant specification discloses reducing bone resorption in an individual. The instant specification discloses treating osteoporosis, which is characterized by low bone mass and/or decreased bone mineral). However, the instant claims' recitation, "a method for reducing bone resorption" in an individual exhibiting low bone mass or decreased bone mineral density" renders the claims broader than the original disclosure. The recitation now can read on treating other diseases such as bone cancer. An individual suffering from bone cancer would exhibit low bone mass and/or decreased bone mineral. The instant claims change the scope of disclosure and the scope of that which was contemplated at the time of filing and resulting in new matter. The specification as filed does not provide a written description or set forth the metes and bounds of this "limitations".

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide specific written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
9/21/07

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER

AU 1647 9/24/07